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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/549,463	04/14/2000	Guus Hatteboer	4038.1US	8657

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EXAMINER	
MITRA, RITA	
ART UNIT	**PAPER NUMBER**
1653	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Feb 03/04

Office Action Summary	Application No.	Applicant(s)	
	09/549,463	HATTEBOER ET AL.	
	Examiner	Art Unit	
	Rita Mitra	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-7,11,13,14,73-86 and 96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-7,11,13,14,73-86 and 96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 April 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

File Copy

DETAILED ACTION

Election/Restriction

Applicants' election without traverse of Group I, claims 1, 3, 5-7, 11, 13, 14, 73-86 and 97 in paper #15, filed on August 8, 2002 is acknowledged. Applicants have also selected Influenza virus for the selection of viral protein. Therefore, claims 22 and 88-96 are withdrawn under 37 C. F. R. 1.142 (b) from further consideration by the Examiner, as being drawn to a non-elected invention. Therefore, claims 1, 3, 5-7, 11, 13, 14, 73-86 and 97 are pending and are under consideration in the instant application.

Objection to Claims

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 88-97 have been renumbered as 87-96 respectively.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6 and dependent claims 3, 5, 7, 11, 13, 14, 76 and 73-75, 96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a proteinaceous substance in a cukaryotic cell comprising providing a eukaryotic cell having a nucleic acid sequence that encodes one adenoviral E1A protein and with a gene encoding a recombinant proteinaceous substance (human erythropoitein); does not reasonably provide enablement for a method using functional homologue, fragment or derivative of adenovirus E1A protein. The specification does

not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

There are no indicia that the present application enables the full scope in view of the structure corresponding to E1A protein functional homologue, fragment or derivative thereof as discussed in the following stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is encompassed.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include: 1) the nature of the invention; 2) the breadth of the claims 3) the amount of direction or guidance presented; 4) the presence or absence of working examples; 5) the quantity of experimentation necessary; 5); 6) the predictability or unpredictability of the art; 7) the state of the prior art; and, 8) the relative skill of those skilled in the art;

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

1) the nature of the invention:

The nature of the invention is defined by the claims, which include a process for the production of a proteinaceous substance in eukaryotic cell using a gene construct, having nucleic acid sequence that encodes one adenoviral E1A protein or a functional homologue, fragment or derivative thereof and with a gene encoding a recombinant proteinaceous substance. Claims 1, 6 and the dependent claims 3, 5, 7, 11, 13, 14, 76 and 73-75, 96 thereto are directed to a process for the production of a proteinaceous substance in eukaryotic cell using a gene construct, having nucleic acid sequence that encodes one adenoviral E1 protein or a functional homologue, fragment or derivative thereof and with a gene encoding a recombinant proteinaceous substance. The specification, however, only discloses cursory conclusions (see page 8), without data to support the findings, which state that the invention provides a method for enhancing production of a recombinant proteinaceous substance in a eukaryotic cell, including providing the eukaryotic cell with a nucleic acid encoding at least part of the proteinaceous substance,

wherein the coding sequence is under control of a CMV-promoter, an E1A promoter or a functional homologue, derivative and/or fragment of either and further providing the cell with E1A activity or E1A-like activity. Further, it is known that E1A expression enhancement is a characteristic of several other promoters. For the present invention, such promoters are considered to be functional homologues of E1A promoters. However the specification does not provide the information on the structure and function of the claimed E1A protein variants. The specification and claims do not set forth the types of changes that can occur to the E1A protein sequence nor provide any guidance as to what positions in the sequence varies and still provides E1 like activity.

2) the breadth of the claims:

The breadth of the claims is broad and encompasses an unspecified number of variants regarding the adenovirus E1A protein as biological active fragments, which are not specifically described or demonstrated in the specification. The specification at page 8 states that the invention provides a method for enhancing production of a recombinant proteinaceous substance in a eukaryotic cell, including providing the eukaryotic cell with a nucleic acid encoding at least part of the proteinaceous substance, wherein the coding sequence is under control of a CMV-promoter, an E1A promoter or a functional homologue, derivative and/or fragment of either and further providing the cell with E1A activity or E1A-like activity. Further, it is known that E1A expression enhancement is a characteristic of several other promoters. For the present invention, such promoters are considered to be functional homologues of E1A promoters. The specification also indicates at page 8, lines 21-27 that the E1A effect can be mediated through the attraction of transcription activators, the E1A promoter or homologue thereof and/or through the removal/avoiding attachment of transcriptional repressors to the promoter. The binding of activators and repressors to a promoter occurs in a sequence dependent fashion. Claims 1, 6, 7 and 96 require a functional derivative and or fragment of an E1A promoter or homologue thereof, therefore at least includes the nucleic acid binding sequence of at least one E1A protein regulated activator and/or repressor. However, the disclosure fails to provide a description of a promoter that demonstrates an E1A expression enhancement

or a functional derivative or a fragment that includes the nucleic acid binding sequence of E1A protein regulated activator or repressor. Therefore, as the specification fails to describe adequately the structure and function of those E1A variants, one skilled in the art would not recognize a specific utility for the variants and would not know how to use them. Thus, for the reasons set forth above, undue experimentation is required to make and use the claimed E1A variants. Furthermore, the claim 1 requires a eukaryotic cell that does not encode a structural adenoviral protein in its genome or a sequence integrated therein. It is known that tumor viruses exist in an integrated or free state within the transformed cells. Frequently multiple copies of viral DNAs are found, however specification has not provided any description for the integrated DNA. The position of the integration is not described nor it is known whether this DNA represents complete or defective genome. Therefore, it would require undue experimentation to determine the position of the integration and the status of the integrated DNA.

Claims 77-86 depend from claims 1 and 6 where the proteinaceous substance comprises a viral protein other than an adenoviral protein. The viral protein selected for the current prosecution is an influenza virus neuramidase and/or a hemagglutinin. Specification at page 19, lines 11-13 indicates that cells which include adenoviral E1 sequences, preferably in their genome are capable of producing the viral protein in significant amounts, however, the specification fails to provide a description or a demonstration in support of this statement. Although the specification outlines art-recognized procedures for producing viral protein using adenoviral E1A variants, this is not adequate guidance as to the nature of functional derivatives that may be constructed. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitution can be made with a reasonable success are limited. Certain positions in the sequence are critical to the protein's structure and function relationship, such as various sites directly involved in binding. Thus, further experimentation is required to make and use the claimed invention.

As for factors 3-5:

3) the amount of direction or guidance presented;

4) the presence or absence of working examples; and

5) the quantity of experimentation necessary:

No description or Examples are provided of the claimed variants. Because of the limited information in the specification it would require undue experimentation since no specific description is provided about the structure of E1A variants. No activity of those variants have been demonstrated. Without more guidance from the specification it would require undue experimentation for a person having skill in the art to make and use the claimed variants.

As for factors 6-8:

6) the predictability or unpredictability of the art

7) the state of the prior art

8) the relative skill of those skilled in the art:

The invention is highly unpredictable for the reasons set forth for factors 1-5. The prior art has shown that the (Setoguchi et al. Blood, vol. 84 (9), pp2946-2953, November 1, 1994) a recombinant adenovirus AdMLP.Epo construct having human Epo gene when introduced into human hepatocyte cell line Hep3B resulted in a 15-fold increase in Epo production in 24 hours (see section below of 102(b) rejection). As indicated by the studies conducted by Setoguchi, in-vitro expression of AdMLP.Epo and also the in-vivo animal models are not predictive in the assessment of expression of erythropoietin using E1A variants. The general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the structure and function for E1A variants.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because in summary, the scope of the claim is broad, the working example does not demonstrate the claimed variants, the guidance/the teaching in the specification is limited, and the outcome is unpredictable for the various modified forms, it is necessary to have additional guidance and to carry out further experimentation to

assess the property of the variants. Therefore, due to large quantity of experimentation necessary to determine an activity or property of the disclosed process using adenovirus E1A and the variants thereof, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of modification on E1A protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and /or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 3, 5, 7, 11, 13, 14, 73 and 76-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because of the use of the phrase "or a sequence integrated therein" (line 7). It is unclear as to whether or not it refers to "a nucleic acid sequence" in line 1 or whether it refers to some other undefined sequences. Also unclear is where the line 7 is integrated, is it in the genetic material encoding the E1 protein or the eukaryotic cell genome? Claims 3, 5, 7, 11, 13, 14 and 76-86 are included in the rejection because they are depended on rejected claim and do not correct the deficiency of the claim from which they depend

Claims 7, 11, 73 and 81-86 are indefinite because of the use of the term "and/or." It is not clear whether the word followed by "and/or" is included or not. Claims 79 and 84 are included in the rejection because they are depended on rejected claim and do not correct the deficiency of the claim from which they depend. Deletion of "and/" or "/or" is suggested.

Claim 81 lacks antecedent basis as the claim is directed to a method of producing human recombinant protein, which has no basis in claim 7.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 5, 6, 7, 11, 13, 14, 73, 74, 75, 76 and 96 are rejected under 35 U.S.C. 102(b) as being anticipated by Setoguchi et al. (Blood, vol. 84 (9), pp2946-2953, November 1, 1994). Setoguchi et al. teach a recombinant adenovirus AdMLP.Epo construct by deleting the majority of E1 from adenovirus type 5, and replacing E1 with an expression cassette containing the adenovirus type 5 major late promoter (MLP) and the human Epo gene (see Abstract). Setoguchi et al. further demonstrated infection of human hepatocyte cell line Hep3B with AdMLP.Epo that resulted in a 15-fold increase in Epo production in 24 hours (see Abstract, Materials and Methods at page 2946, col 2, page 2947, col 1 and 2; and Fig 1 and Fig 2), thus anticipating claims 1, 3, 5, 6, 7, 11, 13, 14, 73, 74, 75, 76 and 96 of instant application. Setoguchi et al.'s recombinant molecule in cultured human hepatoma cell line Hep3B (ATCC HB8064) is considered for the eukaryotic cell of claims 1 and 6 because the claim requires a eukaryotic cell (human cell in claim 6) having a nucleic acid sequence encoding at least one adenoviral E1 protein or a functional homologue, fragment or derivative thereof, a gene encoding a recombinant proteinaceous substance (a human recombinant protein in claim 6), culturing said cell in a suitable medium and harvesting at least one proteinaceous substance (human recombinant protein in claim 6) from said cell. Further Setoguchi's eukaryotic cell is considered for the mammalian cell of claim 3 and for the human cell of claim 76, wherein the human Epo gene of Setoguchi is considered for the gene encoding a proteinaceous substance of claims 5, 11 and 73 and erythropoietin of claims 13, 14 and 74,75 of the instant

application. The partially deleted E1 of Setoguchi's construct is considered for the fragment or derivative of E1A protein of claims 1, 6, 7 and 96.

Therefore, claims 1, 3, 5, 6, 7, 11, 13, 14, 73, 74, 75, 76 and 96 of the instant application are being anticipated by Setoguchi et al.

Conclusion

No claim is allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rita Mitra whose telephone number is (703) 605-1211. The Examiner can normally be reached from 9:30 a.m. to 6:30 p.m. on weekdays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr.Christopher Low, can be reached at (703) 308-2923. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CHRISTOPHER S. F. LOW
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Rita Mitra, Ph.D.
November 16, 2002